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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	20

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
989,896	GEHRMANN et al
Examiner	**Group Art Unit**
SAUNDERS	1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 11/7/00 & 1/5/01.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 1-22, 25-33 is/are pending in the application.

Of the above claim(s) 14-22 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 1-13, 25-33 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☑ Claim(s) 1-22, 25-33 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 18

☐ Interview Summary, PTO-413

☐ Notice of References Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

The request filed on 2/7/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/989,986 is acceptable and a CPA has been established. An action on the CPA follows.

The request for filing of a CPA (Paper 17) has requested entry of the after final amendment filed on 1/5/01 (Paper 14) and has also provided a preliminary amendment (Paper 19). Following entry of both these amendments, the claims pending are 1-22 and 25-33.

Since the request for filing a CPA indicated that applicant was requesting a continuation application, the election of Group I carries through to this CPA application. Claims 1-13 and 25-33 are under examination.

The preliminary amendment of Paper 19 amended non-elected claims 18 and 20-22. Though these have been amended to depend from claim 1 the encompassed subject matter is still, nucleic acids, vectors, cells and animals containing a nuclei acid. These claims therefore remain with Group II and are withdrawn; claims 14-22 are withdrawn from prosecution.

Claims 1-13 and 25-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing by virtue of inconsistently reciting "at least one antigen binding region" (lines 1-2) and also "the antigen binding region has a bivalent or a multivalent structure" (lines 3-4). Instead of reciting "at least one" at line 1, applicant must recite--two or more--, in

order to render the claim internally consistent and also consistent with the specification's definition of a bivalent or multivalent structure (page 2, last paragraph).

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 5 is not enabled by virtue of reciting "the 24-25 kDa glycoprotein defined by Mab L6".

It appears that the practice this embodiment of the invention the L6 antibody, or another antibody to the same antigen must be available. There is no evidence on the record that such is the case. Applicant may overcome this rejection by any of the following:

1) showing that one knew how to obtain the recited glycoprotein without use of the L6 antibody --e.g. without the use of immunoprecipitation or of immunoaffinity chromatography;

2) showing that an antibody to the recited antigen was publicly available as of applicant's filing date--e.g. available commercially or by virtue of public accession resulting from the issuing of a patent; or

3) assuming the hybridoma secreting the 1-6 antibody was in applicant's possession, depositing the hybridoma in accord with 37 CFR 1.801-1.809.

Note, the examiner can find numerous U.S. patents reciting an L6 antigen/antibody; however it is not clear that these pertain to the same L6 monoclonal antibody. Applicant is requested to supply a U.S. reference.

Claims 1-13 and 25-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims reciting constructs having the specifically exemplified linkers, does not reasonably provide enablement for claims encompassing any and all linkers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Applicant's traverse of the 103 rejection has admitted on the record that one could not provide the linkers of the claimed construct without undo experimentation. Therefore no claim is considered enabled unless it is limited to recite the sequence of the linkers used in the example.

As set forth in more detail, in the response to applicant's traverse of the 103 rejection, it is not clear whether applicant considers the linkers internal to the sFv or the linkers fusing the sFv to the enzyme to be critical to the invention. Until the record has been clarified, the examiner considers the 112 scope of claims rejection to apply to both the internal linkers and the fusion linkers; thus the sequence of each of these must be recited in the claims.

Claims 1-9, 25-27 30, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al (Brit. J. Cancer 65, 235, 1992) or Seeman et al (EP 0,501,215, English equivalent is CA 2,062,047) in view of Huston et al (5,132,405) and as necessary Bosslet et al (EP 0,040,097, English equivalent is US 5,591,828) and Eaton et al (EP 0,392,745).

The Bosslet et al and Seeman et al primary references have essentially the same disclosure showing a fusion protein comprising an Fab (derived from a humanized version of anti-CEA antibody 431), a linker, and a human B-glucuronidase. This protein differs from that instantly

claimed by virtue of having an Fab (composed of H and L chains) instead of having an antigen binding region compound of a single polypeptide (e.g. an sFv) formed from VH and VL segments. Huston et al teach that such an antigen binding region may be present in multiple copies (col. 4, lines 21-36 and col. 9, lines 29-31) and that the antigen binding region(s) may be fused to other functional molecules such as enzymes (col. 3, line 66-col. 4, line 4; col. 8, lines 4-6 and col. 9, lines 1-28). When the fusion polypeptide is expressed in a eukaryotic host (Huston et al at col. 11, lines 19-20 and col. 16, lines 1-7) one would have expected the polypeptide to be glycosylated in accord with instant claims 2 and 9.

The essence of the obviousness rejection is that it would have been obvious to modify the fusion protein constructs of the primary reference by substituting the single chain antigen binding polypeptides of Huston et al for the Fab of the construct of Bosslet et al or Seeman et al. Motivations to make this substitution are as follows:

1) Huston et al teach enzymes can be fused to the antigen binding region(s). One would have hence fully expected the glucuronidase enzyme taught by Bosslet et al or Seeman et al to be useable when fused to the single chain constructs of Huston et al.

2) One of ordinary skill in the art would have recognized Fab, Fv and the single chain constructs of Huston et al as functional equivalents in terms of antigen binding. See Huston et al at col. 3, lines 42-52; col. 19, lines 9-30. Note also that Eaton et al teach sFv fragments may be used as the antigen binding entity in conjugates containing prodrug activating enzymes.

3) One would have been motivated to use the sFv of Huston et al in lieu of Fab since the former can have increased stability, and can penetrate tissues more rapidly than antibodies or their conventially produced fragments. See col. 4, lines 10-20.

4) One would have been motivated to provide the constructs of Huston et al with two or more antigen binding regions because such would increase the overall affinity/avidity of the protein when binding to cell surfaces that present multiple copies of the antigen. See Huston et al at col. 4, lines 21-37. See Bosslet et al ('097) at Fig. 3 and discussion associated therewith for a teaching of how a polypeptide can be provided with two oppositely oriented antigen binding regions within a single polypeptide.

5) From the above considerations set forth in parts 3) and 4) one would have expected that, due to the lower size of sFv compared to Fab, one would have been able to provide a construct that has at least bivalency for antigen (as opposed to monovalency when one provided an Fab) without significantly increasing the size of the construct over that containing an Fab. One would have thus gained the above noted advantage of increased affinity/avidity without significant loss of tissue penetrating capacity of the polypeptide.

6) One would have expect an inherent advantage to be gained by using the single chain constructs of Huston et al in that one would only need to transfect cells with one instead of two vectors in order to obtain expression of the protein. Compare Huston et al at col. 18, lines 5-31 with Bosslet et al at page 235, col. 1, last paragraph.

As to the limitations set forth in dependent claims that have not been implicitly or explicitly addressed supra note the following.

Claims 25 and 33 are directed to a pharmaceutical composition and method of treatment. The Bosslet et al disclosure teaches potential therapeutic use (page 238). Seeman et al likewise teach use of the fusion proteins in humans (page 1). The above noted portions of Huston et al teaching improved tissue penetration clearly have a body treatment in consideration. Thus claims 25 and 33 would have been obvious.

Claim 26 is drawn to a diagnostic composition or use thereof. This claim recites merely an intended use that carries no weight and does not distinguish the polypeptide from what it would be in any composition in which it would bind to antigen and have enzymatic activity. Clearly such compositions would include those wherein the binding and enzymatic activity of the polypeptide is evaluated --e.g. Bosslet et al at pages 235-236, Huston et al at col. 19.

Claims 27 and 30 require that the prodrug activating enzyme be a beta-lactamse, which is taught by Eaton et al as a prodrug-activating enzyme. They further point one to use of this enzyme obtained from B. Cereus (page 4, line 14).

Claims 1, 11-12 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al or Seeman et al in view of Huston et al and as necessary Bosslet et al and Eaton et al as applied to claim s 1-9, 25-27, 30 and 33 above, and further in view of Ong et al (Cancer Res. 51, 619, 1991), Bagshawe et al (WO 89/10140), and Huston et al (Methods Enzmol., 204,46, 1991.

The above stated rejection of claim 1 was based upon teachings of the production of a fusion polypeptide without particular consideration of the host cell to be employed for its expression. Only in the case of claims 2 and 9 did the examiner point to the use of eukaryotic cells, which would have been expected to provide glycoslyation.

Huston et al (methods . . .page 70) teach that polypeptides containing sFv may be secreted into the periplasmic space of Gram-negative bacteria and be properly refolded with the correct disulfide bonds. Since E.Coli are more easily grown than many eukaryotic cells, such as myeloma cells, one would have been motivated to use an E. Coli expression system capable of providing correctly folded proteins in large amounts. One of ordinary skill would have recognized that polypeptides produced by E.Coli would not be glycosylated.

Ong et al teach that it is advantageous to permit rapid clearing of circulating therapeutic antibodies in a treated individual be providing galactosyl moieties on the antibodies. These authors particularly teach that such clearing would be advantageous in cases wherein antibody-enzyme conjugates that convert a prodrug to an active drug are employed. Since, as noted supra in the rejection of claim 1, antibody-enzyme conjugates and sFv-enzyme fusion proteins are functionally equivalent it would have been obvious to provide galactosyl moieties on sFv-enzyme fusion proteins, so that these could be rapidly cleared from the circulation. One of ordinary skill would have known that when a polypeptide is expressed in a prokaryote, such as E. Coli (taught by Huston et al methods . . ., at page 70) there is no glycosylation, and hence, such an expressed

polypeptide could be subsequently glycosylated with galactose moieties according to a chemical method, such as that taught by Ong et al (page 1620), col. 1).

Bagshawe et al will also be relied upon for teaching the desirability of placing galactosyl and/or mannosyl moieties on an antibody that is a member of an antibody-prodrug activating enzyme conjugate. See page 9, lines 1-5 and page 10, lines 6-25. The blocking and clearing strategy taught therein is akin to that taught by Ong et al at pages 1622-1624. From the teachings on Ong et al and Bagshawe et al, either together or each alone, one would have ample motivation to provide galactosyl or other carbohydrates residues taught by Bagshawe et al (page 13) on sFv-enzyme fusion proteins.

Claims 1, 10, 13 and 29 are rejected under U.S.C. 103(a) as being unpatentable over Bosslet et al or Seeman et al in view of Huston et al and as necessary Bosslet et al and Eaton et al and further in view of Ong et al, Bagshawe et al and Huston et al as applied to claim 1, 11-12, and 32-33 above, and further in view of Goochee et al (Biotechnol, 9, 1347, 1991).

The above rejections have noted that one would have realized that it would have been desirable to provide a galactosylated or mannosylated polypeptide in order to enhance clearance of unbound peptide from the circulation.

Goochee et al at page 7 show that it was known that yeast could be used to express polypeptide having a high degree of mannosylation and having a rapid clearance rate. It hence would have been obvious to express the polypeptide of claim 1 in such yeast in order to provide polypeptide having mannose moieties that would allow for effective clearance of the polypeptide.

The species recited in claim 13 is specifically taught by Goochee et al at page 1348. The species recited in claim 29 is not specifically taught at page 1348; however, Goochee et al teach most yeast strains provide such mannose moieties and it would have been within the ordinary skill of one in the art to determine which yeast species and strains would be appropriate.

Claims 1 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al or Seeman et al in view of Huston et al and necessary Bosslet et al and Eaton et al as applied to claims 1-9, 25-27, 30 and 33 above, and further in view of Bagshawe et al (WO 88/07378).

Bagshawe et al show the further feature that it was known and conventional to provide carboxypeptidase G2 from pseudomonas as a prodrug activating enzyme in antibody enzyme conjugates fro therapy.

The above statement of the 103 rejections follow what was previously set forth in Papers 6 and 10. Applicant's urging of record in Papers 9, 12 and 14 have been considered but are unconvincing of patentability over the above cited prior art.

First of all the examiner notes that the traversals have focused on the unpredictability of choosing appropriate linkers to arrive at the claimed construct. However the record has become muddled, due to a confusion as to just what linker is being discussed. It is to be noted that there are two different linkers in the claimed fusion protein. The first of these linkers is that within the sFv domain, which links a VH and VL, or visa versa. This is the linker discussed by Huston et al (methods) at pages 50-55. The second linker is that which would link the sFv domain to the enzyme domain. This is analogous to the linker that links the Fab and enzyme in the constructs of

Bosslet et al (Brit J Cancer) or Seeman et al. To the extent that applicant considers design of the latter linker to be critical to the invention, the examiner notes that only dependent claim 8 even requires the presence of such a linker.

In order to avoid further confusion in the record, applicant must specifically point out which of these two linkers is being considered.

With respect to the first of these linkers (internal to sFv) , the prior art provides adequate teachings with respect to its length and design. See, for Example, Huston et al (5,132,405 at col.8, line 53-60 and Huston et al (Methods) at pages 52-44.

With respect to the second of these linkers (fusion linker), the prior art teachings of Bosslet et al (Brit J. Cancer,), and Seeman et al provide one with reasonable direction. See for example, Seeman et al at page 3, lines 24-27 and page 6, line 8-page 7, line 14. Therein Seeman et al teach use of an immunoglobulin hinge region, and applicant's own disclosure (page 4) has contemplated likewise and added nothing more precise with respect to the nature of what particular hinge might be appropriate to overcome any problems.

Note that the examiner considers that one of ordinary skill would have naturally been led to include the hinge linker of Bosslet et al or Seeman et al when substituting an sFv fragment for an Fab fragment. Further, one would have expected this hinge region to provide an appropriate linker of either an Fab or a sFv domain to the enzyme, particularly in the case where the linker connects the C-terminal of the sFv to the N-terminal of the enzyme.

With respect to applicant's arguments presented on 11/15/01 in Paper 14, it is unclear whether applicant considers one would not have know how to choose the linker internal to sFv or the linker that fuses the sFv and enzyme. Applicant's discussion of the Brocklehurst e-mail and the Perham et al article would apparently relate to linkers joining two or more domains of a fusion protein. These references however are unconvincing of unpredictability with respect to linking an sFv to an enzyme. The reader has no idea what two proteins one was attempting to fuse in the case of the Brocklehurst e-mail. The Perham et al article pertains to fusing multiple enzymes which must act together in an assembly line manner in which the product of a first enzyme must lie in proximity to a second enzyme etc. This situation is different from the case of an sFv-enzyme fusion protein in which the sFv provides no product which is then acted upon by the enzyme.

The Fremont et al article pertains to various means of constructing soluble TcR receptors, wherein in same constructs the Va and VB domains are joined by an unspecified linker (analogous to the instant linker internal to sFv?). This article reports use of such linkers gave materials which may not have been properly refolded. The article, however, does not convince that choosing the appropriate linkers to construct an sFv domain involves undue experimentation, given the above noted teaches by both Huston et al references pertaining to such linkers and given the fact that the claims issued to Huston et al. did not specify particular linkers.

Applicant's response filed on 11/7/00 (Paper 12) has urged that Huston et al does not exemplify a prodrug activating enzyme and that these enzymes have a different behavior from other proteins. Applicant has not stated what this "different behavior" is that would render it unpredictable as to whether these fusion proteins would be functional. It is noted that Huston et al (5,132,405) teach fusion of sFv to enzymes in general, and one of ordinary skill would not have expected a prodrug activating enzyme to be anymore difficult to fuse in active form than other enzymes in a fusion protein.

Applicant has further argued that Huston et al do not exemplify a sFv fragment that binds tumor antigens and that "tumor antigens are more difficult to work with and behave differently than other antigens" (page 7). Applicant has not explained what the differences between tumor antigens and other antigens are; thus the statement is of no probative value. The examiner can only guess that applicant may mean that tumor antigens on cells may be in a cryptic form and thus sometimes fail to bind antibody. Whatever might be the nature of tumor antigens does not detract from the teachings of Huston et al with respect to the provision of sFv constructs which would be capable of binding thereto, once the tumor antigen has been exposed from its cryptic form. Applicant has then merely argued that one would not have been able to generalize from Huston et al's generalized teachings of fusion proteins as to whether such would be capable of activating prodrugs (pages 7-8) but has offered absolutely no reason as to why prodrug activating enzymes in general would be inactive after fusion to an sFv domain.

Applicant raises the issue of possible antigenicity of the linkers (page 8); however this issue need not be addressed since there is no claim limitation that requires applicant's construct to lack immunogenicity due to the introduction of linkers, nor has applicant provided any teachings in his own disclosure of how to avoid this problem (let alone even a mention of such a problem). Applicant's claims are thus considered to encompass constructs which may contain immunogenic linkers.

Applicant's response then focuses on isolated instances of case, discussed at page 55 of Huston et al (methods) wherein sFv binding affinity and/or specificity is compromised due to the presence of the linker internal to sFv. Applicant is reminded that these isolated teaching do not detract from the overall teachings of Huston et al, and applicant is reminded that the claims of Huston et al (5,132,405) are presumed to be valid and therefore practicable without undue experimentation. Applicant is further reminded that, even if there are same cases in which it may be difficult to provide an sFv of adequate affinity (affinity retention is not a feature of applicant's claims), an absolute predictability of success is not required. Only a reasonable expectation of success is required. In re O'Farrell 7 USPQ 2d 1673.

Applicant's response at pages 9-10 state that linker design appears to be the limiting factor in sFv construction and then cited, pages 52, 54, and 55 of Huston et al (Methods) which, as noted supra refer to the linkers internal to sFv, applicant then goes on to state (page 10, lines 1-2) 'Thus Huston et al provides evidence that linker design is critical for fusion of sFv molecules to other proteins". Here applicant is confusing the record, because Huston et al's teachings concern

the internal linkers, while applicant appears to be referring to the fusion linker. Applicant's argument's must precisely print out which linker is intended, in any further responses. Finally, with respect to the issue of linkers (whether internal linkers or fusion linkers), applicant has presented no claim which specifically recites the sequence(s) of the exemplified linkers, which applicant has argued could not have been arrived at from the prior art. Applicant's arguments are thus not commensurate with claim scope.

Applicant's discussion of the tertiary (secondary) references by arguing Bosslet et al do not teach sFv. This reference was not relied upon for such a teaching.

Applicant has argued deficiencies in the Eaton et al reference concerning degradation products, but has not pointed out specifically where this teaching is found. The examiner is thus unable to comment further, but still considers the reference to have established β-lactamase as a known prodrug activating enzyme in the immunconjugate therapy art.

Applicant has argued that Ong et al teach antibodies, not sFv constructs, but has offered no reasons as to why one would not have expected Ong et al's methods to work with sFv, nor any reason why one would not have been led, according to the rational of the rejection to make the invention according to teachings of the combination of references. Applicant has offered no reason why the presence of linker's in sFv would prevent the possibility of or teach away from the conjugation of galactose moieties thereto.

Applicant has argued Bagshawe et al teach that the first component should have no galactosyl residues. Applicant is incorrect and is referred to page 10, line 3-6, teaching a first component conjugate having added galactosyl residues.

Applicant's discussion of Goochee et al is unconvincing that the reference is inapplicable. To merely state that Goochee's teaches glycosylation in yeast is significantly different from that in mammals, does nothing to make use of the reference improper. Applicant further argues that p.132, teaches against the use of yeast to produce proteins for human therapy. However applicant has left out the qualification that this teaching pertains to proteins for which one desires a long circulation time. The combination of references applied by the examiner was based on the fact that one would desire to have rapid clearance of the administered fusion protein, and Goochee et al (paragraph spanning page 1352) confirm that yeast produced proteins would be expected to undergo rapid clearance.

Applicant's arguments filed on 11/7/00 and on 1/5/01 have been considered but are unconvincing of patentability.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, Ph.D. whose telephone number is (703) 308-2976. The examiner can normally be reached on M-F from 8:15 to 4:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Saunders:mv

May 21, 2001

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644